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GM-611 Chugai Pharmaceutical Theo L Peeters

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GM-611 is an erythromycin derivative that acts as an agonist at the motilin receptor. It is being developed by Chugai as a potential treatment for gastric motility disorder [169036], as well as reflux esophagitis, non-ulcer dyspepsia and diabetic gastroparesis [347963]. GM-611 is in phase II trials in the US for reflux esophagitis [322624], [347955], [399349].

GM-611 acts by a novel mechanism whereby it stimulates and promotes peristalsis in the stomach and other segments of the gastrointestinal tract [334994]. The drug was shown to produce a dose-dependent sustained depolarization of rabbit duodenal smooth muscle. Depolarization appeared to be associated with activation of monovalent cation-selective channels [273336].

In December 2000, Credit Suisse First Boston predicted that successful development of GM-611 could lead to sales over \$500 million [400228].

Introduction

GM-611 is an erythromycin derivative which stimulates gastrointestinal motor activity [240411] and has potential in the treatment of gastric motility disorders, reflux esophagitis, non-ulcer dyspepsia and diabetic gastroparesis [169036], [347963]. It is a member of the motilide class of compounds, which originated from the discovery that erythromycin mimics the effect of the natural peptide, motilin [240413]. Besides GM-611, which is currently in phase II clinical trials, several congeners, including ABT-229 (Abbott Laboratories), EM-574 (idremcinal; Kitasato Institute/TAP Pharmaceuticals Inc) and KC-11458 (Solvay SA), have been developed by other companies. An extensive review can be found on the Internet (<http://www.med.kuleuven.ac.be/gih/motilid.htm>).

Synthesis and SAR

In comparison with erythromycin, GM-611 and other motilides contain an enol. In fact, 8,9-anhydroerythromycin A 6,9-hemiacetal may be considered the parent molecule of all motilides, with the introduction of the enol moiety enhancing the molecule's affinity for the motilin receptor [52180], [240416]. In addition, the 12-hydroxyl group is methylated so as to prevent acid-catalyzed conversion to poorly active spiroacetals [164427]. An analog feature is present in ABT-229, whereby the 12-hydroxyl moiety is absent. It is known that substitution of the amino function of the desosamine sugar also affects affinity for the motilin receptor and, in contrast to the two methyl groups present in erythromycin A, GM-611 has a methyl and an isopropyl group. GM-611 is identical in this respect to EM-574. The other feature of GM-611 is the modification at position 11, where the hydroxyl group has been oxidized to a ketone. GM-611 is synthesized from 2'-O-acetyl-4'-O-formyl-8,9-didehydroerythromycin A 6,9-hemiacetal [170227].

Originator Chugai Pharmaceutical Co Ltd

Status Phase II Clinical

Indication Gastric motility disorder

Action Motilin agonist

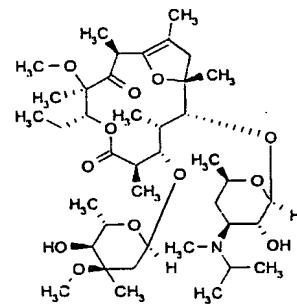
CAS Erythromycin, 8,9-didehydro-N-demethyl-9-deoxy-6,11-dideoxy-6,9-epoxy-12-O-methyl-N-(1-methylethyl)-11-oxo-

Registry No: 154738-42-8

Note: GM-611 free base

CAS Erythromycin, 8,9-didehydro-N-demethyl-9-deoxy-6,11-dideoxy-6,9-epoxy-12-O-methyl-N-(1-methylethyl)-11-oxo-, (E)-2-butenedioate (2:1)

Registry No: 154802-96-7



Pharmacology

Motilides are motilin receptor agonists [198080], [240419], which has also been confirmed for GM-611. In the most frequently used model, the rabbit duodenum, the potency of GM-611 to induce tonic contractions is comparable to the potency of other motilides such as ABT-229 [362987] and EM-523 (Kitasato Institute/Shimizu Seiyaku Co Ltd/Takeda Chemical Industries Ltd) [362989], and is about 4-fold less than the potency of motilin [362989]. The effect of GM-611 is blocked by the motilin antagonist GM-109 (Chugai Pharmaceutical Co Ltd) [362987]. An electrophysiological study showed that motilin and GM-611 both caused sustained depolarizations of intestinal smooth muscle associated with the activation of monovalent cation-selective channels and a reduction of the amplitude of spike potentials due to an inhibition of voltage-dependent Ca^{2+} channels [243661].

There is increasing evidence for the existence of motilin receptor subtypes and motilides could have some selectivity towards them. In the chicken, GM-611 has an effect on the proventriculus, but not on the ileum, although motilin produces a response in both tissues [362989]. This may indicate that, at least in this species, GM-611 preferentially activates the neural motilin receptor, as the effect of motilin on the proventriculus is neurally mediated, while the effect on the ileum is a direct smooth muscle effect. It should be noted, however, that even in the ileum the potency is rather weak (about 1000-fold less than motilin). It has been claimed that in the rabbit colon GM-611 binds with equal affinity to a synaptosomal or a microsomal preparation [382326].

An *in vivo* study in conscious Rhesus monkeys has indicated that GM-611 potently stimulates gastric emptying at doses of 0.01 to 3 μM [158616]. In addition, this study demonstrated a greater potency of GM-611 in comparison to cisapride (0.1 to 1 $\mu\text{M}/\text{kg}$). In an acetaminophen assay in dogs, GM-611 at doses of 0.1 mg/kg and 1 mg/kg (iv) significantly accelerated gastric emptying [170227].

Metabolism

No data are currently available on the metabolism of GM-611.

Toxicity

No data are currently available on the toxicity of GM-611.

Clinical Development

Phase I

Phase I trials commenced in the US at the end of 1998 [399033], but no data are currently available.

Phase II

Phase II trials are ongoing in the US and Canada [339349].

Side Effects and Contraindications

No data are currently available.

Current Opinion

The number of therapeutic agents available to treat hypomotility disorders such as gastroparesis, pseudo-obstruction and constipation is limited. Recently it was even further reduced, at least in the US, by the withdrawal of the 5-HT₄ agonist cisapride because of its cardiac side effects [399404]. Therefore motilides, which have a completely different mechanism of action than existing prokinetics, and which have the further advantage of mimicking the effects of the natural hormone motilin, may have potential as prokinetic agents. Moreover, the parent compound, the well-known antibiotic erythromycin, has been used successfully for a variety of clinical conditions although it is less potent than the newer motilides such as GM-611 [240424].

The development of ABT-229, a congener of GM-611, however, was stopped [383364] because it was unable to relieve symptoms in patients with functional dyspepsia, and even demonstrated a tendency to aggravate symptoms [399260]. This led Abbott researchers to conclude that motilides will not be of use in the treatment of gastroparesis, and that acceleration of gastric emptying is not the right therapeutic goal. However, tachyphylaxis, which was observed to an extreme degree in an animal study with ABT-229, may have reduced its efficacy to zero. Additionally, the pharmacological profile of motilides may differ, especially with regard to their potency towards the different motilin receptors. Therefore, it will be important to verify whether GM-611 differs from ABT-229 in causing tachyphylaxis and in activating different subtypes of motilin receptors. There is an indication that GM-611 prefers neural receptors in the chicken [362989], although in this species motilin and its receptor differ from the mammalian receptor. In mammals, the muscle receptors for motilin and GM-611 appear to be identical [362987].

Even in the absence of a difference in pharmacological profile, it should be noted that the neural motilin receptor, which presumably increases antral contractility leading to accelerated gastric emptying, has a higher affinity for motilin than the smooth muscle receptor [399261], which may increase fundic tone leading to early fullness and satiety. Therefore, as an experimental study with erythromycin suggested, high doses may activate both smooth muscle and neural receptors, and low doses only the neural population [382277]. This certainly corresponds with the fact that antibiotic doses of erythromycin cause gastrointestinal side effects, while much lower doses are required to accelerate gastric emptying and bring relief in patients with severe gastroparesis [240243]. Careful studies over a range of doses may therefore be required to assess the potential of GM-611.

Development history

Developer	Country	Status	Indication	Date	Reference
Chugai Pharmaceutical Co Ltd	US	C2	Gastric motility disorder	26-APR-99	322624

Literature classifications

Chemistry

Study Type	Result	Reference
Synthesis	Synthesis of GM-611 from 2'-O-acetyl-4'-O-formyl-8,9-didehydroerythromycin A 6,9-hemiacetal.	170227

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
In vitro	Mechanism of action.	Rabbit duodenum smooth muscle. Contractile experiments, patch-clamp and intracellular recording.	Depolarization, decrease of the amplitude of spikes. EC_{50} for contractility = 11.9 nM.	243661
In vitro	Mechanism of action.	Contractility of rabbit duodenal segments.	Increase in tone. EC_{50} = 32 nM.	362987
In vitro	Binding affinity for neural and smooth muscle receptors.	Subcellular preparations from rabbit colonic smooth muscle tissue.	Similar affinity for synaptosomes and microsomes.	382326
In vitro	Mechanism of action.	Contractility of chicken proventriculus and ileum, and rabbit duodenum.	No effect in chicken ileum. Weak neurally-mediated effect in chicken proventriculus. EC_{50} = 72 μM .	362989

Biology (continued)

Study Type	Effect Studied	Experimental Model	Result	Reference
In vivo	Gastropointokinetic activity.	Gastric emptying in conscious Rhesus monkey	Gastrointestinal motility stimulated by GM-611 0.01 to 3 μ mol/kg iv. Also stronger acceleration of gastric emptying rate by GM-611 compared to cisapride (0.1 to 1 μ mol/kg).	158616
In vivo	Gastropointokinetic activity.	Acetaminophen assay in dogs.	Significant acceleration of gastric emptying at 0.1 mg/kg iv and 1 mg/kg po	170227

Associated patent

Title Erythromycin derivatives for the treatment of intestinal motility disorders.

Assignee Chugai Seiyaku KK

Publication WO-09803531 29-JAN-98

Priority JP19960225806 24-JUL-96

Inventors Ishitani Y, Takata S, Ishigai M, Nishigori Y.

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• Results presented show that GM-611 stimulates gastrointestinal motility and gastric emptying rate in conscious monkeys.

164427 Potent, acid-stable and orally active macrolide-type motilin receptor agonists, GM-611 and the derivatives. Koga Hiroshi, Sato Tsutomu, Tsuzuki Kochi, Onoda Harumi, Kuboniwa Hitoshi, Takanashi Hisanori BIOORG MED CHEM LETT 1994 4 11 1347-1352

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• Careful and in depth study of the mechanism of action of motilin and GM-611 in rabbit duodenum. The most extensive study available on this topic.

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347955 Fuji Gotemba to provide biotech products worldwide: Dr Yamazaki of Chugai. PHARMA JPN 1999 1672 1-4

347963 Chugai: R&D pipeline. Chugai Pharma Europe Ltd COMPANY WORLD WIDE WEB SITE 1999 November 15

• Web page detailing Chugai's R&D pipeline

362987 Erythromycin derivatives ABT 229 and GM 611 act on motilin receptors in the rabbit duodenum. Clark MJ, Wright T, Bertrand PP, Bornstein JC, Jenkinson KM, Verlinden M, Furness JB CLIN EXP PHARMACOL PHYSIOL 1999 26 3 242-245

• Confirms that motilides act on motilin receptors.

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• Characterization of motilin receptors in the chicken and comparison with the rabbit.

382277 Involvement of two different pathways in the motor effects of erythromycin on the gastric antrum in humans. Coulie B, Tack J, Peeters T, Janssens J GUT 1998 43 3 395-400

• Study comparing the effects of high and low doses of erythromycin, leading to a model of high affinity neural and low affinity smooth muscle receptors.

382326 Neural and muscular receptors for motilin in the rabbit colon. Miller P, Trudel L, St Pierre S, Takanashi H, Poitras P PEPTIDES 2000 21 2 283-287

• Evidence solely based on binding studies of two motilin receptors in rabbit colon.

383364 Drug Development Pipeline - Abbott Laboratories discontinues development of ABT-229. Abbott Laboratories COMPANY COMMUNICATION 2000 September 25

• Tina Brookhouse, Pharmaceutical Communications, Abbott Laboratories, stated that ABT-229 was no longer in development.

399033 Drug development pipeline - GM-611. Chugai Pharmaceutical Company Ltd COMPANY COMMUNICATION 2001 February 15

• Mr Tadasu Ohbu, GM-611 Global Project Leader, stated that phase I trials of the drug commenced in the US in 1998 and that no data have been published.

399260 Lack of antidiarrheal effects of the macrolide gastrokinetic (GK) agent, ABT-229, in functional dyspepsia (FD) and idiopathic gastroparesis (IG). Talley N, Verlinden MH, Snape W, Beker JA, Ducrotte P, Dettmer A et al GASTROENTEROLOGY 2000 118 A847

• Abstract detailing a phase II study with ABT-229. Presumably data from this study were important in the decision by Abbott to stop development of this congener of GM-611.

399261 Concentration-dependent stimulation of cholinergic nerves or smooth muscle by [Nle13] motilin in the isolated rabbit gastric antrum. Van Assche G, Depoortere I, Thijs T, Janssens J, Peeters TL EUR J PHARMACOL 1997 337 267-274

• An extensive study comparing smooth muscle and neural effects on motilin.

399349 Drug development pipeline - GM-611. Chugai Pharmaceutical Co Ltd COMPANY COMMUNICATION 2001 February 19

• Mr Tadasu Ohbu, Global Project Leader for GM-611, confirmed that GM-611 is in phase II trials in the US and Canada.

399404 Cisapride withdrawn due to cardiac side effects. PHARM J 2000 265 7107 152

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